SEATTLE PROSTATE INSTITUTE
1101 Madison Street Suite 1101
Seattle, WA 98104
P 206-215-2490
www.seattleprostate.com

# PCa Commentary

**Volume 75 May – June 2012**

***A special issue on "Magnetic Resonance Imaging in Prostate Cancer"***

PAGE CONTENTS



**Ed Weber, M.D.**
**Editor**

Your comments and requests for information on a specific topic are welcome at
**ecweber@nwlink.com**

## MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING - Emerging as the New Standard for Staging Prostate Cancer.

Reviewed by Jim Borrow, M.D., Staff Radiologist, First Hill Diagnostic Imaging, Seattle.

The venerable pelvic CT scan is no longer capable of meeting the increasingly sophisticated requirements for accurate local staging of prostate cancer, tumor localization within the prostate gland, and predicting future cancer behavior. As a strictly anatomical study, it images only the most gross examples of extracapsular extension, seminal vesicle involvement, and lymph node spread. Its usefulness in these areas is clearly dismissed by Abdellaoui et. al. in their review "Imaging in Prostate Cancer" (*Future Oncology,* 2011):

> "Computed tomography (CT) plays no role in the diagnosis of primary prostate cancer, but is useful in staging systemic disease in lymph nodes, bone and distant organs. ... Although there has been improvement in CT resolution, ... its resolution remains inadequate to evaluate the prostate zonal anatomy and its relationship with adjacent structures."

The same conclusion is held by Hricak, Scardino et al. (*Radiology*, 2007, April).

> "Although CT continues to be widely used in patients with newly diagnosed prostate cancer it has virtually no role in prostate cancer detection or primary staging."

## MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING

Multiparametric imaging of the prostate combines the anatomical imaging strength of the standard T1 and T2-weighted sequences with one or both "functional" imaging techniques, e.g., diffusion-weighed MR (DW-MR) and dynamic contrast-enhanced MR (DCE-MR). T1 and T2-weighted sequences already have been shown to be superior to CT in demonstrating prostate zonal anatomy and defining extracapsular extension and seminal vesicle involvement. The addition of one or both of these options to T1 and T2-weighted sequences increases the performance of MR in tumor localization and identification. Uniquely, the capacity of DW-MR and DCE-MR to estimate tumor tissue density and vascularity allows assessment of cancer grade and aggressiveness. From these data an estimate can be made regarding a tumor's likely future behavior.

MR has an established role in patients who are at intermediate- or high-risk for localized disease progression where accurate information about the extent of local disease is required for optimal treatment planning. It also can guide in selecting patients suitable for active surveillance. *Because of the confounding effect of blood in MRI interpretation it is recommended that the study be delayed by 6-8 weeks after biopsy*.

**continued**

## STANDARD T1 and T2-WEIGHTED MR IMAGINING

The basis of MR's discrimination of anatomical structure is its sensitivity to the water content of tissue.

"The sensitivity of MRI in detecting extracapsular extension or seminal vesicle invasion has improved to a range of 73 to 80% with a high specificity of 97-100%. In comparison, the accuracy of CT for identifying malignancy in seminal vesicles is 58-64%."

Extracapsular extension as small as 0.5 mm at histopathology has been accurately detected (Abdellaoui, ibid). This accuracy is serviceable to surgeons in their consideration of nerve-sparing procedures. In a study of preoperative MRI using an endorectal coil, "Hricak et al. [*Cancer* 100(12)2004] demonstrated that MRI findings changed the surgical plans in 78% of patients and was accurate in 93% of patients."

## DIFFUSION-WEIGHTED MR IMAGING

Diffusion-weighted imaging builds upon the information from the T2-weighted sequence and measures the freedom of movement of water molecules through tissue.

Compared to the dense and irregular packing of cells in malignant tumors, the normal prostate's relatively looser structure of glands and tubules allows relatively freer passage of water molecules. The cancer's greater density impedes this diffusion. Many studies have confirmed that increasing tissue density correlates with higher Gleason grades, allowing DW-MR to offer an estimation of the degree of cancer aggressiveness. Diffusion-weighted imaging lacks spatial resolution, however when augmented with the greater anatomical accuracy of the T2W data, cancer identified is further enhanced.

Diffusion-weighted imaging is particularly useful for tumor identification in the peripheral zone, but is less so in the normally denser tissue in the central and transitional zones. Whereas water molecules move freely in the looser glandular tissue of the peripheral zone, the denser normal tissue in the central and transitional zones decreases the freedom of water movement. This smaller differential gradient between normal and malignant tissue diminished MR's ability to discriminate between the two. The technical term describing this diffusion gradient is the "apparent diffusion coefficient (ADC)."

DW-MRI is fast, adds only a small amount of time to a study of the prostate, and does not require the use of a contrast agent. However, it is very motion sensitive and is disturbed by materials that alter the local magnetic environment, such as hip prostheses.

## DYNAMIC CONTRAST-ENHANCED MR IMAGING

DCE-MRI employs gadolinium-based MRI contrast agents. It visualizes tissue vascularity.

The convoluted vascular network and the increased vessel wall permeability associated with tumor angiogenesis offer a distinctive signature compared to normal vasculature. The contrast accumulates more rapidly in malignant tissue and correspondingly "washes out" faster. The fast serial imaging sequences of DCE allows a graphic representation of this malignant signature in comparison to the vascular characteristics of normal tissue.

continued

**DYNAMIC CONTRAST-ENHANCED MR IMAGING continued:**

DCE-MRI sequences, when supplemented with T2-weighted data, have improved the detection of extracapsular extension with a reported

- sensitivity of 86%
- specificity of 95% and
- negative predictive value, 93%
- yielding an overall staging accuracy of 95% (Bloch et al., *Radiology*, 2007 Oct).

Interestingly, the additional of DCE-MR to the combination of T2W/DW-MR imaging decreases the sensitivity and specificity of MR in the detection of central and transitional zone tumors. In the peripheral zone the combination increases tumor detection, a significant advantage since the great majority of cancers are located in this zone.

Therefore the sequence combination for detecting
peripheral zone tumors is T2W + DW + DCE and for the
central/transitional zone cancers is T2W + DW-MR.

**BOTTOM LINE:**

Standard magnetic resonance imaging with T1 and T2-weighted sequences, augmented by diffusion-weighted and dynamic contrast-enhanced sequences, currently offers optimal accuracy in identifying the location and extent of malignancy in the prostate gland and in detecting extracapsular extension.

## IMAGING PROSTATE CANCER METASTATIC TO BONE

For men with high-risk prostate cancer appropriate management depends on an accurate assessment of clinical evidence of bone involvement. The most informative imaging study is an MRI of the axial skeleton (MRIas).

The report by Lecouvet et al. (*JCO*, Aug 2007) comparing the effectiveness of axial MRI with other detection strategies remains the most definitive analysis. In their study:

- high risk was defined as biopsy Gleason score ≥8 and PSA ≥20
- Sixty-six men were studied: 26 were newly diagnosed, 12 showed PSA recurrences within 3 years after surgery and had PSA doubling times <12 months, and 28 showed PSA rises while on androgen deprivation therapy with doubling time <12 months.

The "standard work-up" consisted of a technetium bone scan (BS) augmented by targeted X-Rays as needed (TXR), with further clarification in 17 men with MRIas requested at the physician's discretion. All 66 underwent axial MRI. "In the absence of a histologic gold standard, we used, as the best valuable comparator, a panel of reference consisting of CT correlation of equivocal MRI findings, prospective systematic follow-up BS and MRI studies at 6 months, and clinical and biologic follow-up obtained at 6 months of follow-up."

RESULTS: Based on the best reference comparator, metastatic spread was diagnosed in 41 men (66%). "MRIas was significantly more sensitive than any other approach."

continued

**IMAGING PROSTATE CANCER METASTATIC TO BONE continued:**

- "*Sensitivities* were 46% for BS alone, 63% for BS/TXR, 83% for BS/TXR/MRI [in the 17 men for which MRIas was requested], and 100% for MRIas [performed in all 66 men]."
- *The specificities* were 32%, 64%, 100%, and 88% respectively.
- Thirty percent of men judged *negative* in the standard work-up, and 47% whose evaluation was equivocal were found positive on MRIas, "which altered the initial planned therapy."

As stated by Lecouvet, "The superiority of MRI lies in its ability to detect cells seeded into the normal hematopoetic marrow and its fat cells, thus identifying bone metastases at an early stage before osteoblastic reaction becomes visible on BS and/or TXR."

There is often concern that limiting imaging to only the spine would miss a diagnosis of metastatic disease in men whose metastases were isolated to non-spinal locations. This issue was most recently addressed by Wang and Shen in "Study on the distribution features of bone metastases in prostate cancer" (*Nucl Med Comm,* Apr 2012). They analyzed the location of 2000 bone lesions. Only 1.2% of these lesions were found isolated to the appendicular skeleton and not accompanied by evidence of metastases in the spine.

Lecouvet et al., in their study of 60 patients with prostate cancer at high risk of metastases, compared whole-body MRI with the imaging of only the axial spine (*Eur Radiol*, 2010). Conclusion: "There were no patients with isolated "peripheral" metastases at WB-MRI missed at AS-MRI."

**BOTTOM LINE:** A single MR study of axial spine is the most accurate and efficient method for the earliest detection of bone metastases in men at high risk for spread of cancer.

## FERUMOXTRAN-10: An Unapproved Contrast Agent for MR Lymphography - Promising Clinical Potential; Unexpected Biology.

*Why write about a MR contrast agent that is unapproved in the US? ...*

... Because multiple European studies of MR Lymphography provide important clinical guidance in two areas that are *poorly served* by conventional CT and MRI scanning: e.g., in initial staging for evaluation of nodal spread; and at restaging when salvage radiation to the prostate bed is being considered to address PSA progression after primary surgery.

Ferumoxtran-10 is the generic name for "Sinerem" (Guerbet Pharmaceuticals, Paris, France) which belongs to the class of "Ultra Small superParamagnetic Iron Oxide nanoparticles" (USPIO). These particles are avidly ingested by tissue macrophages.

USPIOs are formulated to maximize uptake in the macrophages residing in lymph nodes, benign and malignant, but also concentrate in the macrophages of the liver, spleen, and bone marrow. When used in conjunction with MR imaging the technique is termed MR Lymphograhy.

continued

**FERUMOXTRAN-10 continued:**

Ferumoxtran-10 is very similar to "Combidex," the contrast agent that made such a splash in the 2003 NEJM article by Harisinghani which reported its ability to detect nodal metastases as small as 0.5 cm. For various reasons, Combidex did not receive FDA approval.

Interestingly, a newer formulation of the same class of agents is marketed in the US under the name "Feraheme," FDA approved for the treatment of iron deficiency anemia. By taking advantage of the FDA "off-label" provision, Sand Lake Imaging, Orlando, Florida, utilizes Feraheme for MR Lymphography.

## BACKGROUND:

A quote from an editorial by Harisinghani in *Lancet Oncology*, Sept 2008, emphasizes the clinical importance of accurate lymph node imaging:

"Despite presumed curative surgery in patients with prostate cancer, almost one-third of patients relapse," [principally those with intermediate- and high-risk disease]. The absence of scrupulous presurgical lymph-node staging is one factor contributing to this high amount of relapse."

Heesakkers, another researcher studying MR Lymphography, introduces his report by stating

"The detection of nodal metastases is of utmost importance to determine prognosis and choice of treatment in patients with prostate cancer." "Prostate Cancer: Detection of Lymph Node Metastases Outside the Routine Surgical Area with Ferumoxtran-10-enhanced MR Imaging," *Lancet,* May 2009.

Heesakker's data confirms the already-known understanding that in prostate cancer there is considerable "atypical" lymph node spread, i.e. nodal spread beyond the customary template for pelvic lymph node dissection (PLND).

He found that 41% of men at intermediate-to-high risk for nodal metastases harbor positive nodes outside this customary dissection region.

Conventional CT and MRI scanning, depending as they do on size-based criteria, are woefully inadequate in detecting malignancy in lymph nodes.

In a study by Briganti et al., *Eur Urol,* Nov 2011, which examined the efficacy of CT scanning to identify nodal metastases, only 32.8% of nodes judged positive on CT were histologically confirmed at extended PLND.

"In patients with a nomogram-derived LNI [lymph node involvement] risk of ≥50%, sensitivity, specificity, and accuracy [for detection of malignancy] was only 23.9%, 94.7%, and 50.3%."

USPIO MR LYMPHOGRAPHY is based on metabolic features as opposed to size criteria, and aims to address this deficiency. The Harisinghani's 2003 *New England Journal* article ("Noninvasive detection of clinically occult lymph-node metastases") reported research on Ferumoxtran-10 that showed a sensitivity of 100% and a specificity of 96% in the detection of patients with nodal involvement, not only in the pelvis but also in the abdominal nodal region. The negative predictive value of MR Lymphography is a very reassuring 96% (Heesakkers, *Lancet Oncology,* Sept 2008).

continued

**FERUMOXTRAN-10 continued:**

## MACROPHAGE BIOLOGY: The foundation for MR Lymphography.

The predilection of macrophages to ingest iron oxide is the basis of MR Lymphography. The USPIOs are not aggregated in the malignant prostate cells themselves; however, the malignant tumors within the node attract and concentrate macrophages, termed "tumor associated macrophages" (TAM). The number of TAMs within a tumor increases proportionally with increases in the size and aggressiveness of the cancers with which they commingle.

*The areas of lymph nodes infiltrated with malignant cells and their associated TAMS have been architecturally altered and do not show the uptake of ferumoxtran-10.* By 24 hours after I.V. injection, ferumoxtran-10 has been internalized by normal functioning nodal macrophages. Magnetic resonance detects the signal difference resulting from the unequal iron oxide concentration in normal macrophages in the uninvolved portion of a node compared to the cancer/TAM composite. This constitutes the basis for detection of nodal malignancy by MR Lymphography.

Subversively, TAMs themselves secrete signals that deflect the host immune attack on their host cancers.

The details of this unique biology were elegantly researched by Heike Daldrup-Link, Stanford Molecular Imaging Program, and presented in *Clin Cancer Res*; July 2011, "MRI of Tumor-Associated Macrophages with Clinically Applicable Iron Oxide Nanoparticles." She concludes that in addition to facilitating identification of malignancy in lymph nodes, USPIOs "may serve as a new biomarker of long-term prognosis, [guide] related treatment decisions, and [may facilitate] the evaluation of new immune-targeted therapies."

## POTENTIAL CLINICAL APPLICATIONS FOR MR LYMPHOGRAPHY:

The difference between "estimation" and knowledge brings to mind Robert Frost's poem,

"The Secret Sits"
"We dance round in a ring and suppose,
But the Secret sits in the middle and knows."

1. The decision regarding the appropriateness of prostatectomy in patients with intermediate- and high-risk disease rests upon knowledge of lymph node spread. MR Lymphography can accurately inform this decision. Conversely, a negative MR lymphogram could obviate the need for an initial staging PLND.

This was studied by Abdollah et al. (*BJUI,* Aug 2011). He notes that "The National Comprehensive Cancer Network guidelines recommend pelvic lymph node dissection in patients with a nomogram-predicted lymph node risk of 2% or more," and some recommendations suggest a PLND only for those men whose risk is >5%.

His analysis estimates that, for example, if a PLND is carried out in only those men whose risk exceeds 4% then positive nodes will be missed in twenty-six percent of men who did not have the procedure*. His conclusion: the accuracy of staging with MR Lymphography, particularly its high negative predictive value, circumvents the uncertainties inherent in relying on these estimates.*

continued

**FERUMOXTRAN-10 continued:**

## POTENTIAL CLINICAL APPLICATIONS

2. "Salvage" radiotherapy, given adjuvantly or as deferred therapy, is frequently considered in men with stage ≥pT3 cancer with worrisome features. Unfortunately, the criteria are inadequate for selecting for treatment only those men who would benefit. Consequently, salvage treatment is curative in only 35% of recipients.

Zietman, Harisinghani et al. (*Clinical Imaging,* 2009) report the usefulness of MR Lymphography to inform this decision in "Lymphotropic nanoparticle-enhanced magnetic resonance imaging (LNMRI) identifies occult lymph node metastases in prostate cancer patients prior to salvage radiation therapy."

MR Lymphography was performed in 26 men post-radical prostatectomy whose PSAs rose to >0.2 and ≤4.0 ng/ml at a median of 38.3 months after surgery.
- Lymphography was positive in 6 and the positive nodes were
  pre-sacral in 2; peri-rectal in 2;
  para-aortic in 1, obdurator/external iliac in 4.

The nodal diameters were between 3 - 5 mm in 6 of the 9 positive nodes.

At a median [insufficiently long, they concede] follow-up of 8.9 months "none of the patients with a negative LNMRI have evidence of prostate cancer." A larger trial was called for, but to date has not occurred.

3. In patients with a high risk of nodal involvement (in the Roach radiation study >15% risk was the criteria) undergoing primary radiotherapy the jury is still out as to whether the toxicity of radiation therapy to the "whole pelvis" is worth the small gain in outcome as compared to irradiation of the prostate only.

Meijer et al. offer examples of the application of MR Lymphography to clarify whom to treat what to target:

*"Magnetic resonance lymphography-guided selective lymph node irradiation in prostate cancer"* (Int J Radiat Oncol Biol Phys, 2012 Jan). They present 4 patients at high risk of nodal spread who had no enlarged nodes on CT or MR scans, but whose MR Lymphography revealed positive nodes.

Their conclusion: "This information could be used to delineate a boost volume and to individualize the pelvic target volume for elective irradiation. They acknowledge that whether their approach will improve outcome will need to be established by further clinical studies.

**BOTTOM LINE:** Accurate and selective contrast agents to identify malignancy in lymph nodes would be useful in planning optimal management for men with prostate cancer at high risk for nodal spread.

Visit us at:
www.seattleprostate.com
News & Events
This month's issue plus a compilation of past articles is available online.